



Seroepidemiology and Risk Factors of Hepatitis B Virus Infection: A Population-Based Azar Cohort Study

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Abstract

Background: Hepatitis B is a major global health problem. It can cause chronic infections and put people at high risk of death from cirrhosis and hepatocellular carcinoma. The aim of this study was to report the epidemiological features of hepatitis B virus (HBV) infection and risk factors based on the data from Azar Cohort.

Methods: The population of this study comprised the people in the age range of 35-70 yr from Azar cohort, East Azerbaijan Province, Iran between 2015 and 2016. Based on cluster sampling, 4,949 people were selected and invited to complete the questionnaire and perform the tests. Blood samples were analyzed for serum HBV markers (HBsAg, HBsAb and HBcAb) by ELFA method. The data were analyzed using SPSS statistical software.

Results: The mean (SD) age of the participants was 49.15 ± 9.02 years. The frequency rates of HBsAg, HBsAb and HBcAb were estimated as 1.03%, 16.9% and 24.95%, respectively. There was statistically significant association between family history of hepatitis ($P < 0.001$) and jaundice history ($P < 0.001$) with the presence of HBsAg. There was also a positive correlation between marital status ($P = 0.002$), history of hospitalization ($P < 0.001$), smoking ($P = 0.001$), dental procedures ($P < 0.001$), foreign travels ($P = 0.005$), occupation status ($P = 0.002$) and the presence of HBcAb.

Conclusion: The frequency of hepatitis B in Azar Cohort was 1.03% which is a lower rate compared with other reports from Iran. The association of the population studied and the increase of public awareness in this area can probably prevent this disease.

Keywords: Hepatitis B virus; Seroepidemiology; Iran

Introduction

Viral hepatitis is a common infectious disease usually manifested by symptoms of liver inflammation. One of the most common types of hepatitis is viral hepatitis B. The Hepatitis B virus (HBV) is estimated to have contaminated more than two billion people worldwide and about 360 million are chronic HBV carriers (1).

Most of these people do not get advanced complications during their life, even though the 15%-40% rate of chronic infections presents a potential risk for the development of severe forms of diseases such as cirrhosis, liver failure and hepatocellular carcinoma (2, 3). The WHO's Global Health Sector Strategy on viral hepatitis targets include 65% reduction in HBV-related deaths,

90% reduction in new infections and a diagnosis of 90% of the infections by 2030 (4).

The frequency of carriers is different in different parts of the world. In Asia, Africa and the Pacific Islands, the infection with hepatitis B is one of the most common causes of death and in North America, Europe and Australia, the frequency of hepatitis B infection is low (5). HBV infection is characterized by five clinical symptoms: acute, chronic, fulminate, asymptomatic and occult infection (6). Acute HBV infection is often asymptomatic and people who suffer from chronic hepatitis B are the main sources of HBV transmission without being aware of their condition. The identification of these individuals can delay or prevent the progression of subsequent complications of the infection (7).

HBV is transmitted through several routes: blood transfusion, surgical history, tattooing, cupping, non-hygienic injection, multiple sexual partners, mother-to-child transmission, mucosal contact with blood and contaminated fluids, history of dental procedures and IV drug users (4). The evaluation of transmission routes can help improve preventive measures and design strategies to control HBV infection. Iran has a low-intermediate status in terms of the frequency of HBV (8). In Iran, between 1991 and 1999, the frequency of HBV infection was reported 1.7%. The frequency for the general population in Iran was 2.1% in the time between 2001 and 2006 (9, 10). The frequency rate of HBV varies in different provinces, in a way that while this rate was 0.76% in Kermanshah, it was 5.1% in Golestan (11). In Iran, about 1,347,000 (range: 1,253,000 – 1,434,000) people are suffering from chronic hepatitis B infection (11). According to a systematic review conducted, the overall frequency of HBV infection in East Azerbaijan Province between 2001 and 2007 was 1.3% (10). In addition, the average frequency of HBsAg among blood donors in the time of 2011-2015 was 0.18% in this Province (11).

Whereas there is a hepatitis B vaccination program for newborns and people at high risk in Iran since 1993, and there is a national health plan to decrease its frequency, new cases of the

disease occur in adolescents and adults (12). The total economic burden of this disease in Iran is significant (13), and that the prognosis is not fulfilled in a good manner, the prevention and identification of this disease not only reduces the number of affected people but also decreases the economic burden on society and the number of disabled individuals.

The main reasons that justify conducting this research study include:

- ✓ Analyzing socio-cultural factors effective in the transmission of hepatitis B infection
- ✓ The lack of a comprehensive study in this area in the Province
- ✓ The fact that most of the previous studies carried out merely on specific groups of people (these groups cannot be regarded as the general population)

Methods

Sample of the Study

In this cross-sectional study, the sample population including both males and females were invited to participate in the study from 2015 to 2016. The method of sampling was cluster sampling, including 50 clusters (of 100 subjects each) from the above county. The study consisted of 5000 individuals in the age range of 35-70. Fifty-one people refused to participate in the study and 4949 final individuals were selected (participation rate: 98.9%). In this cohort study, the first house on the right of the nearest street to the center of Azar Cohort was selected as the first household for each cluster randomly. Then, the stages of the research project were explained to eligible individuals for inclusion in the study and they were invited to carry out the tests and complete the standard questionnaire in the center. The inclusion criteria were lifelong residency in the area, Iranian nationality, ability to answer to the questions and willingness to participate in the study. Meanwhile, the exclusion criteria included physical disabilities such as deafness and blindness, mental retardation and psychosis or those who

did not agree to enter the study or refused to give blood samples.

After obtaining written consent from the subjects, a questionnaire containing epidemiological information and HBV risk factors was completed through face-to-face interviews and then presented to the team of physicians for examination.

At the last stage, 10^{cc} blood sample was taken from each subject. After separation of serum from the blood samples in the cohort laboratory, they were coded and transferred into sterile tubes under a sterile condition and stored in a -80 °C freezer until collection of all the samples.

Measuring the level of HBV markers including HBsAg, HBcAb and HBsAb in serum samples was done by ELFA (Enzyme-Linked Fluorescent Assay) method (Vidas® HBsAg, Biomerieux, France), (Vidas® HBcAb, Biomerieux, France) and (Vidas® HBsAb, Biomerieux, France) respectively. All measuring laboratory equipment was calibrated.

Statistical Analysis

Data are presented as Mean \pm SD and N (%). We used survey data analysis methods to estimate more accurate HBV infection frequency and risk

factors including weighted point estimate frequency rates of HBV biomarkers and their estimated 95% confidence intervals for Qualitative data. Chi-square or Fisher's exact test was used for the comparison of categorical variables. Univariate logistic analysis was used to identify potential influencing factors associated with HBV infection. The factors were selected with $P < 0.1$ in the Univariate model, and a stepwise Multivariate logistic model was conducted to seek the independent risk factors for HBV. A P -value less than 0.05 were considered statistically significant. Statistical analysis was conducted using SPSS (ver.19.0, Chicago, IL, USA).

Results

Characteristics of the Subjects

Overall, 4949 subjects were included in this study. Of 4949 individuals, 2263(45.7%) were males. The mean age of the participants was 49.15 ± 9.02 . Some demographic features and distribution of potential HBV risk factors are shown in Table 1.

Table 1: Some demographic features and distribution of potential HBV risk factors regarding HBV markers¹

Variables	Total	HBsAg Positive	P-value*	HBcAb Positive	P-value*
Gender					
Male	2263 (45.7)	28 (1.2)	0.18	544 (24)	0.17
Female	2686 (54.3)	23 (0.9)		691 (25.7)	
Total	4949	51 (1.03)		1235 (24.95)	
		Marital State			
Unmarried	76 (1.5)	1 (1.3)	0.43	9 (11.8)	0.002
Married	4621 (93.4)	45 (0.97)		1145 (24.8)	
Widow	217 (4.4)	4 (1.8)		68 (31.3)	
Divorced	35 (0.7)	1 (2.9)		13 (37.1)	
		Age group, Y			
< 40	1040 (21)	9 (0.86)	0.94	248 (23.8)	0.43
40-50	1826 (36.89)	18 (0.98)		440 (24.1)	
50-60	1408 (28.45)	17 (1.2)		373 (26.5)	
> 60	675 (13.66)	7 (1.03)		174 (25.73)	
		Occupation status			
Employed	2443 (49.4)	29 (1.2)	0.28	562 (23.0)	0.002
None	2506 (50.6)	22 (0.9)		673 (26.9)	
		Education Level			
No formal educa-	1096 (22.1)	15 (1.4)	0.1	245 (22.4)	0.004

Elementary	1349 (27.3)	15 (1.1)		308 (22.8)	
Mid school	815 (16.5)	6 (0.7)		200 (24.5)	
High school	843 (17)	4 (0.5)		239 (28.4)	
University (Bsc,Msc,Dr)	846 (17.1)	11 (1.3)		243 (28.7)	
			BMI(Kg/m ²)		
Underweight (BMI <18.5)	37 (0.8)	2 (5.4)	0.056	7 (18.9)	0.08
Normal weight (BMI=18.5-24.9)	1080 (22.2)	13 (1.2)		273 (25.3)	
Overweight (BMI=25-29.9)	2136 (43.9)	19 (0.9)		566 (26.5)	
Obese (BMI ≥30)	1612 (33.1)	17 (1.05)		371 (23.0)	
			Use Alcohol		
Yes	561 (11.3)	5 (0.9)	0.72	145 (25.8)	0.6
No	4388 (88.7)	46 (1.04)		1090 (24.8)	
			Smoking Type		
Yes-Daily	616 (12.4)	6 (0.97)	0.99	120 (19.5)	0.001
Occasionally	94 (1.9)	1 (1.06)		30 (31.9)	
No	4239 (85.7)	44 (1.03)		1085 (25.6)	
			Jaundice history		
Yes	85 (1.7)	5 (5.9)	<0.001	30 (35.3)	0.02
No	4864 (98.3)	46 (0.9)		1205 (24.8)	
			History of surgery		
Yes	2931 (59.2)	28 (0.95)	0.53	760 (25.9)	0.056
No	2018 (40.8)	23 (1.13)		475 (23.5)	
			History of Hospitalization		
Yes	3842 (77.6)	40 (1.04)	0.9	1011 (26.3)	<0.001
No	1107 (22.4)	11 (0.99)		224 (20.2)	
			History of Transfusion		
Yes	318 (6.4)	5 (1.57)	0.32	89 (28.0)	0.19
No	4631 (93.6)	46 (0.99)		1146 (24.7)	
			Drug addiction		
Yes	123 (2.5)	2 (1.6)	0.5	24 (19.5)	0.15
No	4826 (97.5)	49 (1.01)		1211 (25.1)	
			History of Dental Procedure		
Yes	2560 (51.7)	21 (0.8)	0.13	721 (28.2)	<0.001
No	2389 (48.3)	30 (1.3)		514 (21.5)	
			Has abnormal Urine test		
Yes	1485 (30)	11 (0.7)	0.18	441 (29.7)	<0.001
No	3464 (70)	40 (1.2)		794 (22.9)	
			Has Foreign Travels		
Yes	2103 (42.5)	28 (1.3)	0.07	567 (27.0)	0.005
No	2846 (57.5)	23 (0.8)		668 (23.5)	
			Has Fatty Liver		
Yes	241 (4.9)	3 (1.2)	0.73	78 (32.4)	0.006
No	4708 (95.1)	48 (1.01)		1157 (24.6)	

¹ Data are presented as No (%);• At 0.05 level, P is significant.

Frequency of HBV Markers

Overall, 51(1.03%) of the subjects were HBsAg positive, 1.2% of whom were males and 0.9% females. The HBc-positive antibody was detected in 1235 subjects, giving an overall prevalence of

24.95%. The frequency rates of Anti-HBc in males and females were 24% and 25.7%, respectively. The highest positive cases of Anti-HBc were in the age group of 50-60 years.

There was a significant difference between education level and Anti-HBc positive ($P=0.004$). Of 4949 subjects 3087 (62.4%) were negative for the whole HBV markers (susceptible to HBV).

Among HBV markers, the frequency of Anti-HBs was significantly different with age groups ($P<0.001$). The highest frequency of HBsAg

(1.9%) was observed among male subjects in the age group less than 40 years. The frequency of HBsAg in the age group of 50-60 yr was higher than other age groups (1.2%), which was not statistically significant ($P=0.94$). Anti-HBs and Anti-HBc were positive in 247 (5%) subjects (Table 2).

Table 2: Frequency of hepatitis B markers among subjects regarding gender¹

<i>Markers</i>	<i>Total</i>	<i>Male</i>	<i>Female</i>
HBsAg(+)	51 (1.03)	28 (1.2)	23 (0.9)
Anti-HBs(+)	837 (16.9)	428 (18.9)	409 (15.2)
Anti-HBc(+)	1235 (24.95)	544 (24)	691 (25.7)
Anti-HBs (+) Anti-HBc(+)	247 (5)	122 (5.4)	125 (4.7)
Anti-HBs(+)/Anti-HBc(-)	590 (11.9)	306 (13.5)	284 (10.6)
Anti-HBs(-)/Anti-HBc(+)	988 (20.0)	422 (18.6)	566 (21.1)

¹ Data are presented as No (%).

Frequency of HBV Risk Factors

There was a significant difference in the frequency of HBsAg and family history of hepatitis and jaundice history. There was a significant relationship between the frequency of Anti-HBc positive and marital status, jaundice history, hospitalization history, dental procedures, foreign travels, occupation status and educational level (Table 1).

Association between HBV Markers and Its Risk Factors

In univariate regression analysis (model a), there was a significant association between jaundice history (OR=6.54) with the presence of HBsAg. There was also a positive correlation between fatty liver (OR=1.46), occupation status (OR=1.22) and the presence of HBcAb.

In model B, all variables with P -value less than 0.1 included in the model regression. In the multivariate logistic regression adjusted with age and sex (model c), Sex (OR=1.31), age (OR=1.19), history of hospitalization (OR=1.49), history of dental procedure (OR=1.54), BMI (OR=1.13), occupation status (OR=1.32) were independent predictors of HBcAb seropositivity (Tables 3, 4).

Discussion

The results of the study showed that the frequency of HBsAg positive was 1.03%. This result was

in line with other results from the Cities of Mashhad (14), Kermanshah (15), Chaharmahal and Bakhtiari Province (16), South Khorasan (17) and Amol (18). According to the study conducted in Golestan Province, the overall prevalence of HBsAg positive was 5.1% in the people of the age range of 18-65 (19). This rate is higher than that of the present study. Differences in these values in various places are attributed to differences in the culture of life, socioeconomic status, population density, place of residence and ethnicity. In recent years, extensive and successful coverage of HBV vaccination in newborns and at-risk individuals has also been effective in reducing the incidence of HBV infection in Iran.

The frequency of HBsAg positive in males was higher than that of females, aligned with both internal (14, 20) and external studies (21, 22). Some risk factors such as injecting drug use, shavings in public barber shops, travels to high-risk areas and high-risk occupations are more prominent in males compared to females, which can justify this difference.

In the distribution of patients with hepatitis B in terms of age group, all age groups were exposed to HBV infection. Most of the patients were in the age group of 50-60 years. In men, the age group less than 40 years (with 1.9%) and in women, the age group of 50-60 yr (with 1.3%)

had the most positive HBsAg results. These results are consistent with the results reported (23, 24). The reason for the high frequency of this age group in our study is probably due to the lack of

vaccination of this age group compared with lower age groups and exposure to hepatitis B risk factors compared with other age groups.

Table 3: Logistic regression for assessing relationship between HBsAg and related risk factors

<i>Variables</i>	<i>OR (95% CI) Model^a</i>	<i>OR (95% CI) Model^b</i>	<i>OR (95% CI) Model^c</i>
Gender			
Male	0.68(0.39-1.20)	-	1.63(0.68-3.91)
Female	-	-	-
Marital State			
Married	1.66(0.79-3.45)	-	-
Unmarried	-	-	-
Age group ,Y	1.09(0.82-1.45)	-	1.19(0.62-2.27)
Occupation status	1.35(0.77-2.36)	-	-
Use Alcohol	0.84(0.33-2.14)	-	-
Smoking Type	1.03(0.67-1.57)	-	-
Jaundice history	6.54(2.53-16.9)	2.33(0.64-8.41)	2.34(0.65-8.40)
History of surgery	0.83(0.48-1.45)	-	1.43(0.72-2.84)
History of Hospitalization	1.04(0.53-2.05)	-	1.57(0.67-3.69)
History of Transfusion	1.59(0.62-4.03)	-	1.55(0.59-4.06)
Drug addiction	1.61(0.38-6.70)	-	1.73(0.36-8.13)
History of Dental Procedure	0.92(0.84-1.05)	-	1.59(0.85-2.97)
Has Foreign Travels	1.65(0.95-2.88)	1.56(0.86-2.81)	1.57(0.86-2.88)
Has Fatty Liver	0.81(0.25-2.64)	-	-

^a Crude Odds Ratio; ^b Adjusted Odds Ratio (all variables with *P*-value <0.1 entered the model); ^c Multivariate logistic regression model adjusted with age and sex

Table 4: Logistic regression for assessing relationship between HBcAb and related risk factors

<i>Variables</i>	<i>OR (95%CI) Model^a</i>	<i>OR (95%CI) Model^b</i>	<i>OR (95%CI) Model^c</i>
Gender			
Male	0.91(0.8-1.04)	-	1.31(1.06-1.62)
Female	-	-	-
Marital State			
Married	0.68(0.55-0.84)	0.87(0.67-1.12)	0.88(0.67-1.15)
Unmarried	-	-	-
Age group ,Y	0.95(0.88-1.01)	-	1.19(1.01-1.39)
Occupation status	1.22(1.08-1.39)	1.03(0.88-1.2)	1.32(1.09-1.60)
Use Alcohol	0.94(0.77-1.15)	-	-
Smoking Type	0.85(0.77-0.94)	0.96(0.86-1.08)	1.32(1.03-1.70)
Jaundice history	0.60(0.38-0.94)	0.64(0.4-1.02)	0.68(0.43-1.08)
History of surgery	0.87(0.77-1.03)	1.07(0.90-1.27)	1.07(0.91-1.27)
History of Hospitalization	0.71(0.60-0.83)	0.80(0.64-0.99)	1.49(1.20-1.86)
History of Transfusion	0.84(0.65-1.09)	-	1.10(0.84-1.43)
Drug addiction	1.38(0.88-2.16)	-	-
History of Dental Procedure	0.80(0.49-1.31)	0.95(0.93-0.96)	1.54(1.33-1.78)
Has Foreign Travels	0.83(0.73-0.94)	0.82(0.72-0.94)	1.13(0.98-1.29)
Has Fatty Liver	1.46(1.11-1.93)	1.28(0.96-1.71)	1.25(0.93-1.67)

^a Crude Odds Ratio; ^b Adjusted Odds Ratio (all variables with *P*-value <0.1 entered the model); ^c Multivariate logistic regression model adjusted with age and sex.

In our study, there was no significant relationship between positive cases and marital status of the participants, but the positive HBsAg in married couples was reported low compared to the single individuals. HBsAg positive cases in married participants were more than single people (16, 25). The frequency of positive cases in single subjects was higher than married ones (26). Although marriage and heterosexual relationships are a major contributor to hepatitis (27), the frequency of HBsAg positive cases was lower in married couples compared to the other people in the present study. To find out the causes of this discrepancy, studies with a comprehensive risk assessment for hepatitis are recommended.

The study of factors associated with HBsAg positive cases indicated that there was no significant relationship between the education level and frequency of hepatitis B. However, illiteracy rate in positive individuals was higher than that of the people having a high-school diploma or high school dropouts. This is in line with other results (20). There was also no significant relationship between education level and positive cases (28).

The lack of information and awareness about the common causes of transmission can be an important factor in this instance, and this raises the role of holding different training courses for such people.

There was no significant difference between the relative frequency of risk factors for hepatitis B including the history of blood transfusion, dental procedures, history of surgery and hospitalization. The dental history correlated with HBsAg positive cases (15). In another study, HBsAg positive had a relationship with transfusion, surgery and IV drug use (16). Based on the published literature in Amol city, there was a significant correlation between the history of surgery and HBsAg positive (18). Moreover, in a study conducted in Zahedan city, no association was observed between HBsAg positive and surgery history (25).

One of the effective factors to prevent hepatitis is related to hospital environment. Realizing the principles and following the standards of health in hospitals, timely sterilization of surgical in-

struments, dental equipment and screening of blood and blood products before use are important in this case. The transmission of the infection may also be related to such routine activities as the use of personal belongings or high-risk sexual behaviors, not studied in our study.

The history of HBsAg positive in one family member and the history of jaundice have been reported as independent risk factors for the transmission of hepatitis B (29). In our study, these factors were also considered as a risk factor for the frequency and transmission of HBsAg positive. This result can be explained by the apparent role of intra-family transmission through continuous contact of a HBV positive person with the other family members.

Such measurements as the improvement of social awareness and public health and the application of disease control strategies through vaccination and treatment have changed the epidemiology of HBV infection in Iran (18).

In the present study, 1235 people (24.95%) out of 4949 participants were positive for HBcAb, which indicates previous infection with HBV. These findings are high compared to other results of the studies (19, 30), though they are similar to other studies (28, 31). There is a heterogeneous pattern in the distribution of Anti-HBcAb in Iranian Provinces. Cultural factors, ethnicities, beliefs and the lack of strict implementation of health guidelines affect the distribution of HBV infection.

Positive HBcAb is a serious threat to the transmission of HBV infection because HBVDNA is measurable in the serum of Anti-HBc positive individuals, which indicates the potential risk of transmission from these individuals to others.

One of the limitations of this study is that it was not possible to prove HBV in HBsAg positive individuals by PCR method due to some resource constraints. The other limitation is related to lack of repeat testing HBcAb positive individuals.

Conclusion

The frequency of hepatitis B in Azar Cohort was 1.03% which is a lower rate compared with other

reports from Iran. A special new program and active training models should be considered to control the high-risk groups of the disease, because the current existing models for the prevention of hepatitis are either out-of-date or inactive.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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